

November 18, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6372-Review.doc).

**Title:** *Helicobacter pylori* and pregnancy-related disorders

**Author:** Simona Cardaropoli, Alessandro Rolfo, Tullia Todros

**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 6372

The manuscript has been revised according to reviewers' suggestions:

1 Format has been updated

2 Revisions have been made according to the suggestions of the reviewer

[02453015]

We thank the Reviewer 02453015 for the suggestions that significantly improved the manuscript.

1. *Some figures or diagrams showing the effect of H. Pylori on pregnancy at varies aspects are highly recommended for this review paper.*

1. We added a schematic figure in order to summarize the correlation among *H.pylori* infection and pregnancy-related disorders (Figure 1).

2. *A guideline should be proposed for the treatment during pregnancy.*

2. We improved the "*H.pylori* INFECTION TREATMENT DURING PREGNANCY" section as requested (pages 10-11).

3. *English still needs to be improved.*

3. English was revised.

[00860822]

1. *As the authors presented and we all know that pregnancy itself can increase the chance of h.p. infection. One thing for this is that there are any evidence on the relationship between pre-pregnancy h.p. infection and pregnancy-associated diseases, or post-pregnancy h.p. infection and the disease association. Of the pre- or post-pregnancy h.p. infection, which is easier to cause pregnancy-related diseases?*

1. We added some considerations about pre- and post-pregnancy h.p. infection in the "Introduction" section (page 3, lines 29-35).

2. *Is there any suggestion on the treatment of pre-pregnancy h.p. infection?*

2. We improved the "*H.PYLORI* INFECTION TREATMENT DURING PREGNANCY" section, as suggested also by reviewer 02453015 (pages 10-11).

3. *If the h.p. infection was treated effectively before pregnancy, whether these patients had a higher risk of re-infection after pregnancy than the normal women?*

3. "Re-infection" is a very interesting point but unfortunately there are no investigations to our knowledge that addressed this specific issue in pregnancy. We added a brief mention in order to highlight this *lacuna* (page 11, line 11).

[01350278]

*"...The summary is too descriptive and no interpretation and commentary statement have been given. In addition the summary is rather in fragments, sometime there is only a single or two sentences for one paragraph (page 4, 5,*

12). *It seems the summary is rather incomplete and did not follow the flow well enough. The organisation of the review is fine. However, some of the statement is not clear enough to go through without looking into the original papers referred.*"

We agree with Reviewer 01350278. Some sentences and paragraphs were not exhaustive, therefore we modified the manuscript following Reviewer 01350278 indications. Specifically:

#### Introduction:

1. *it is better to describe the varieties of Helicobacter pylori antigens and cytotoxins.*
1. We did not disclose the topic of virulence factors, since the only pregnancy-related investigation was performed on CagA and VacA. However, in order to introduce the topic, we added few general information about *H.pylori* virulence factors in the Introduction (page 3, lines 6-18).
2. *how humoral and cell mediated immunity changes in pregnancy increase the susceptibility to the infection?*
2. We edited the paragraph about "*the susceptibility to infection..*" in order to better explain the maternal immunological modifications during pregnancy (page 3, lines 22-28).
3. *how geographic area and socioeconomic conditions affect the detection.*
3. We added two sentences in order to better explain the concept (page 4, lines 2-5).

#### Gastrointestinal disorders in pregnancy:

1. *how multifactorial is the etiology of the HG?*
1. We specified the main conditions related to HG (page 4, lines 26-31).
2. *what is density of H. pylori infection?*
2. We modified the sentence on page 5, line 11 as requested.
3. *what exactly the shift in gastrointestinal pH during early pregnancy?*
3. We changed "shift in gastrointestinal pH" with "reduction of gastric acid production" (page 5, line 16) as suggested.

#### Iron deficiency anemia:

1. *the last paragraph should incorporate ahead within the context.*
1. We moved the last paragraph (page 6, line 11) to lines 33-37 (page 5) as suggested.

#### Preeclampsia:

1. *what is abnormal placentation typical of fetal growth restriction?*
1. In the "Pre-eclampsia" section, we added some key concepts on PE classification in order to clarify the sentence (page 6, lines 20-23). Accordingly, other words in this section were edited (page 6, lines 35 and page 7, lines 1-2).
2. *what exactly the sever inflammatory status referred to?*
2. We did specify it in the following sentence: "... pre-eclamptic women showed higher levels of C-reactive protein, TNF-alpha and maternal leukocytes counts" (page 7, lines 6-7).
3. *what kind of study is require to confirm the hypothesis of H pylori infection as contributory factor in atherosclerosis in PE cases later in life?*
3. We added a sentence at the end of this section (page 7, lines 12-15).

#### Fetal growth restriction:

1. *how maternal appetite impair fetal growth?*
1. Since the term "appetite" is not correct in this context, we modified the sentence "...which in turn may affect maternal gastric absorption and therefore impair fetal growth." (page 7, line 32).

#### Mother-to-child transmission:

1. *what exactly fecal-oral transmission during cohabitation referred to?*
1. We further discussed the hypothesis of *H.pylori* transmission (page 9, lines 15-21) as requested.

Conclusions:

1. *the second paragraph is repetitive, rather than a conclusive remarks.*  
1. We agree with the Reviewer. Therefore, we removed the redundant paragraph (page 11) and added new conclusive statements (page 11, lines 35-38 and page 12, lines 1-7).
2. *the last paragraph is rather a new issues which should be described in details before conclusions.*  
2. We moved and improved this paragraph at the end of "Other pregnancy-related disorders" section (page 9, lines 4-8).
- 3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

A handwritten signature in dark ink, reading "Simona Cardaropoli". The script is cursive and elegant, with a long horizontal stroke at the end of the name.

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